IN THE SPECIFICATION:

Please amend the specification pursuant to 37 C.F.R. 1.121 as follows (see the accompanying "marked up" version pursuant to 1.121):

Please replace the paragraph at page 8, line 21 to page 9, line 6 with:

Various structural features characterize PAMP (GenBank; Accession No. Q92542; SEQ ID NO: 14). The nucleotide sequence (SEQ ID NO: 13) of human PAMP predicts that the gene encodes a Type 1 transmembrane protein of 709 amino acids (SEQ ID NO:14), the protein having a short hydrophilic C-terminus (~20 residues), a hydrophobic transmembrane domain (15-20 residues), and a longer N-terminal hydrophilic domain which contains several potentially functional sequence motifs as listed below in Table 1. The PAMP sequence also contains a Trp-Asp (WD) repeat (residue 226), at least one "DTG" motif (residues 91 - 93) present in eukaryotic aspartyl proteases, as well as several "DTA/DTAE" motifs (residues 480 - 482, 504 - 506) present in viral aspartyl proteases. There are also four conserved cysteine residues in the N-terminal hydrophilic domain (Cys195, Cys213, Cys230, and Cys248 in human PAMP) having a periodocity of 1617 residues, which may form a functional domain (e.g., a metal binding domain or disulfide bridge for tertiary structure stabilization). Subdomains of PAMP have weak homologies to a variety of peptidases. For example, residues 322 - 343, 361- 405, and 451 - 466 have 46% (p = 0.03) similarity to another hypothetical protein; C.

elegans aminopeptidase hydrolase precursor signal antigen transmembrane receptor zinc glycoprotein (SWISS-PROT; World Wide Web (www) expasy.ch/sprot; Accession No. Q93332).

Please replace the paragraph at page 9, line 20 to page 10, line 10 with:

The invention is further based on the identification of conserved functional domains, based on comparison and evaluation of the predicted amino acid sequences of human (SEQ ID NO: 14), murine (SEQ ID NO: 16), *D. melanogaster* (SEQ ID NO: 18), and *C. elegans* (SEQ ID NO: 12) orthologues of PAMP. "PAMP" can be characterized by the presence of conserved structural features, relative to orthologues from *D. melanogaster* and *C. elegans*. Nucleotide sequences encoding homologous hypothetical proteins exist in mice multiple EST, and *C. elegans* (GenBank; World Wide Web (www) ncbi.nlm.nih.gov; Accession No. Z75714; 37% similarity, p = $8.7e^{-26}$) (Wilson *et al.*, *Nature* 1994; 368: 32-38). These hypothetical murine and nematode proteins have a similar topology and contain similar functional motifs to human PAMP. The existence of such homology predicts that similar proteins will be detected in other species including Xenopus, and Zebra fish, to mention a few such possibilities. By comparing the predicted amino acid sequences of human (SEQ ID NO: 14), murine (SEQ ID NO: 16), *D. melanogaster* (SEQ ID NO: 18), and *C. elegans* (SEQ ID NO: 12) PAMP

proteins, we have deduced a series of conserved functional domains. One domain has chemical similarities to cyclic nucleotide binding domains of other proteins, and may have some regulatory role on a potential complex formed between PS1:PAMP and the C-terminal fragment of βAPP, derived either from a- or b-secretase. These putative functional domains are sites for therapeutic target development by deploying drugs which might interact with these sites to modulate βAPP processing via this complex.

Please replace the paragraph at page 38, line 24 to page 39, line 8 with:

The PAMP gene. Chromosomal locations and genetic map positions of the murine and human PAMPS were obtained from public genetic and transcriptional maps (World Wide Web (www) ncbi.nlm.nih.gov). The gene encoding PAMP is located on human chromosome 1 near the genetic markers D1S1595 and D1S2844. The 5′- end of the PAMP gene is embedded in the 5′-end of the coatmer gene encoded on the opposite strand. The human PAMP gene is close to a cluster of markers which have yielded positive, but sub-significant evidence for linkage to or association with Alzheimer Disease in two independent genome wide surveys (Kehoe P, *et al.* Hum Mol Genet 1999; 8: 237-245). The murine PAMP maps within a 700 Kb interval of murine chromosome 1 which contains the gene defect associated with *Looptail* phenotype in mice (Underhill DA,

et al., Genomics 1999; 55: 185-193). Mice heterozygous for *Looptail* show developmental defects in dorsal axial structures including notochord, brain, spinal cord, and somites (Greene ND, *et al.*, Mech Dev 1998; 73: 59-72.), which are reminiscent of those observed in PS1-$^{/-}$ mice (Shen J, *et al.*, Cell 1997; 89: 629-639; Wong PC, *et al.*, Nature 1997; 387:288-292). These observations suggest that the presenilin: PAMP complex may be involved in both βAPP and *Notch* processing.

Please replace the paragraph at page 40, line 20 to page 41, line 12 with:

These results were confirmed in HEK293 cells over-expressing either $\beta APP_{Swedish}$ or the SpC99-βAPP cDNA. The latter encodes the C-terminal 99 residues of βAPP (corresponding to the products of β- secretase cleavage) plus the βAPP signal peptide. The interaction of PAMP appears much stronger with C99-βAPP than that with C83-βAPP. However, C83-βAPP is much less abundant in these cells. In fact, PAMP does interact with both C99- and C83-βAPP stubs. Cumulatively, these results indicate that PAMP likely interacts with the C-terminal derivatives of βAPP which are the immediate precursors of Aβ and p3. However, of greater interest, the genotype of the co-expressed PS1 molecule dynamically influenced the interaction between PAMP and C99-/C83-βAPP stubs. Thus, more C-terminal βAPP fragments co-immunoprecipitated with PAMP in cells expressing

the FAD-associated PS1-L392V mutation compared to cells expressing wild type PS1 (and equivalent quantities of nicastrin and C99-βAPP). Conversely, much less C-terminal βAPP derivatives co-immunoprecipitated with PAMP in cell lines expressing the loss-of-function PS1-D385A mutation (despite the presence of very large amounts of C-terminal βAPP derivatives in these cells). These effects are more easily seen in cells over-expressing the C99-βAPP construct. However, similar but less pronounced differences were also observed in cells over-expressing full-length $\beta APP_{Swedish}$. More importantly, the PS1-sequence-related differences in the interaction of PAMP with C-terminal βAPP derivatives were most evident within 24 hours of transient transfection of PAMP. By 72 hours, the PS1-sequence-related differences were largely abolished. This dynamic change in the interaction of PAMP with C99/C83-βAPP was not due to changes in the levels of PS1, C-terminal βAPP derivatives or PAMP. One interpretation of these results is that the presenilins may be dynamically involved in regulating or loading PAMP with the substrates of β-secretase.